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The purpose of the study was to investigate thermoregulatory and cardiovascular effects of the vasodilatory agent, niacin. Four subjects were studied during rest in a moderately warm environment, ( $T_a = 30 (\pm 1)^\circ\text{C}$ ;  $T_{dp} = 10 (\pm 1)^\circ\text{C}$ ). Esophageal ( $T_{es}$ ) and skin temperature, forearm blood flow and sweating rate were measured twice per min during a 10-20 min period. Heart rate was measured frequently. After control data were obtained, 5 mg niacin/kg<sup>-1</sup> body weight were ingested. Skin temperature increased approximately 15 min after ingestion of the drug, beginning on the head and torso, then spreading caudally. Forearm blood flow, as assessed by venous occlusion plethysmography, increased dramatically, and during

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maximal vasodilation it increased an average of  $9.41 \text{ ml} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$  ( $P < 0.05$ ). Increased dry heat loss after niacin resulted in an average  $T_{es}$  decrease of  $0.47^\circ\text{C}$  ( $P < 0.05$ ). Heart rate was increased an average of 22 beats  $\cdot \text{min}^{-1}$  ( $P < 0.05$ ) after niacin treatment. Marked cutaneous vasodilation persisted for approximately 30 min, then gradually decreased and  $T_{es}$  started to recover. Mean arterial pressure was decreased by 1.6 kPa during niacin treatment (two subjects). In several subjects, sweating rate increased transiently and coincidentally with skin flushing. These data indicate that the cutaneous vasodilatory action of niacin is sufficient to increase markedly dry heat loss in humans resting in a moderately warm environment. However, caution is required in using niacin to increase dry heat loss for two reasons. First, in a moderately warm environment, there was a substantial decrease in  $T_{es}$ ; however, in cool or cold environments, dry heat loss would be even larger than observed in this study and the risk of hypothermia great. Second, any beneficial effect of niacin as a thermoregulatory aid in humans in a moderately warm environment must be balanced against the cardiovascular consequences (increased heart rate and decreased mean arterial pressure) of general cutaneous vasodilation.

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# CARDIOVASCULAR AND THERMOREGULATORY EFFECTS OF NIACIN

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## INTRODUCTION

The vitamin, niacin or nicotinic acid, causes flushing of the skin when taken in large doses. It acts directly on vascular smooth muscle' probably by a mechanism involving a prostaglandin'. The cutaneous vasodilatory action of nicotinic acid is generally considered as an undesired side effect when large quantities of the vitamin are used to treat hyperlipoproteinemia or hyper-triglyceridemia'. Niacin ingestion was reported to decrease core temperature more in three subjects during water immersion ( $T_{water} = 25-30^{\circ}\text{C}$ ) than when immersion was done without niacin'. Niacin increased sensible heat flux (R+C) by increased skin blood flow (SKBF), although skin blood flow and R+C were not quantified in that study. The cutaneous vasodilatory action of nicotinic acid in humans makes it an attractive candidate as a thermoregulatory aid to increase sensible heat flux in environments in which the ambient temperature is less than mean skin temperature. Niacin ingestion increases skin blood flow beginning in the face and spreading to the torso and limbs, which is similar to the vasodilatory effect of atropine. But unlike atropine, the effector function of the eccrine sweat gland is not inhibited. So, it is conceivable that niacin might serve to increase R+C, as does atropine'' but without simultaneously impairing evaporative heat loss from the skin. Before any judgement on whether or not niacin could be used as a thermoregulatory aid is made, its effect on skin blood flow and sensible heat flux must be quantified. Also, the effect of this cutaneous vasodilation on the heart and arterial blood pressure requires investigation. In this study, the thermoregulatory and cardiovascular effects of niacin on resting humans was investigated.

## MATERIAL AND METHODS

Five subjects (three males and two females) volunteered to serve as subjects after they were verbally apprised of the nature and risks of the study. The physical characteristics of the subjects (mean  $\pm$  standard deviation) are as follows: age: 30 ( $\pm 5$ ) years; height: 171.8 ( $\pm 4.1$ ) cm; weight: 67.3 ( $\pm 5.3$ ) kg; and body surface area: 1.77 ( $\pm 0.06$ )  $\text{m}^2$ .

The subjects were completely familiar with all laboratory techniques before the study began. Subjects were studied during rest in a moderately warm environment ( $T_s = 30 (\pm 1)^{\circ}\text{C}$ ;  $P_s = 1 (\pm 0.1) \text{kP}$ ) while in a seated posture. The women were studied in the follicular phase of their menstrual cycles.

Each subject reported to the environmental test chamber after fasting 8-12 h before the experiment. A copper-constantan thermocouple encapsulated in a catheter was swallowed for the measurement of esophageal temperature ( $T_e$ ) and thermocouples

(copper-constantan) were attached to the skin at eight sites". Venous occlusion plethysmography was used to measure forearm blood flow (FBF) " and an automatic blood pressure monitor (Accutorr) was used to determine mean arterial pressure and heart rate.

After all instruments were attached to the subject, a 15 min control period was initiated. During this period, esophageal and skin temperatures, and forearm blood flow were measured every 0.5 min, and blood pressure and heart rate were measured every 2.5 min. Metabolic heat production was measured by open circuit spirometry (Sensor Medics). Five mg niacin per kg body weight was ingested by each subject after the control period. Data were collected after niacin ingestion as was done for the control period.

All data were analyzed by a one way analysis of variance with repeated measures, with the factors being the control period, niacin treatment when FBF was at a peak and niacin treatment when  $T_{es}$  was minimal. Tukey's tests of critical differences were performed when appropriate.

## RESULTS

The onset time of niacin effects was dependent on the individual and averaged 17.8( $\pm 2.5$ ) min. For that reason data were compared statistically at the time of maximal cutaneous vasodilation in the forearm and when  $T_{es}$  was minimal. The pattern of cutaneous vasodilation as indicated by increased skin temperature was regional, beginning in the forehead, then spreading to the chest and back, and finally to the limbs. Mean skin temperature ( $\bar{T}_{sk}$ ) increased 0.5°C by the time of peak FBF ( $p \leq 0.0005$ ) and increased another 0.1°C by the time  $T_{es}$  was minimal (Table 1).

Table 1. Mean ( $\pm SD$ ) thermoregulatory control data, niacin data at peak FBF, and niacin data at the minimal  $T_{es}$ .

	Control	Niacin (peak FBF)	Niacin (min $T_{es}$ )
$\bar{T}_{sk}$ (°C)	34.05 (0.4)	34.58 (0.3)*	34.65 (0.4)*
FBF ( $mL \cdot 100mL^{-1} \cdot min^{-1}$ )	2.90 (1.2)	16.6 (4.4) <sup>b</sup>	10.6 (2.7) <sup>b</sup>
R+C ( $W \cdot m^{-2}$ )	40.10 (5.8)	44.9 (4.5)*	45.4 (3.8)*
$T_{es}$ (°C)	36.73 (0.3)	36.36 (0.4) <sup>b</sup>	36.18 (0.4) <sup>b</sup>
$T_b$ (°C)	36.20 (0.3)	36.01 (0.4) <sup>b</sup>	35.88 (0.4) <sup>b</sup>
MET ( $W \cdot m^{-2}$ )	62.5 (10.2)	67.9 (8.3)	71.5 (7.6)

\*Niacin treatment different from control ( $p \leq 0.0005$ )

<sup>b</sup>All different ( $p \leq 0.0005$ )

FBF increased five-fold at its peak ( $p \leq 0.0005$ ) which averaged 34 min after niacin treatment. By 53 min after niacin treatment, when  $T_{es}$  was minimal, FBF had decreased 6  $mL \cdot 100mL^{-1} \cdot min^{-1}$  from peak, but was still three times greater than control ( $p \leq 0.0005$ ). Radiative and convective heat loss increased 4.7  $W \cdot m^{-2}$  from control to peak FBF, and increased 0.5  $W \cdot m^{-2}$  more when  $T_{es}$  was minimal ( $p \leq 0.005$ ).  $T_{es}$  decreased 0.37°C by the time FBF was at a peak (Table 1) and by 53 min after niacin treatment had decreased 0.55°C ( $p \leq 0.0005$ ).

SUBJECT 1

300 MG NIACIN TAKEN WITH WATER AT 15 MIN

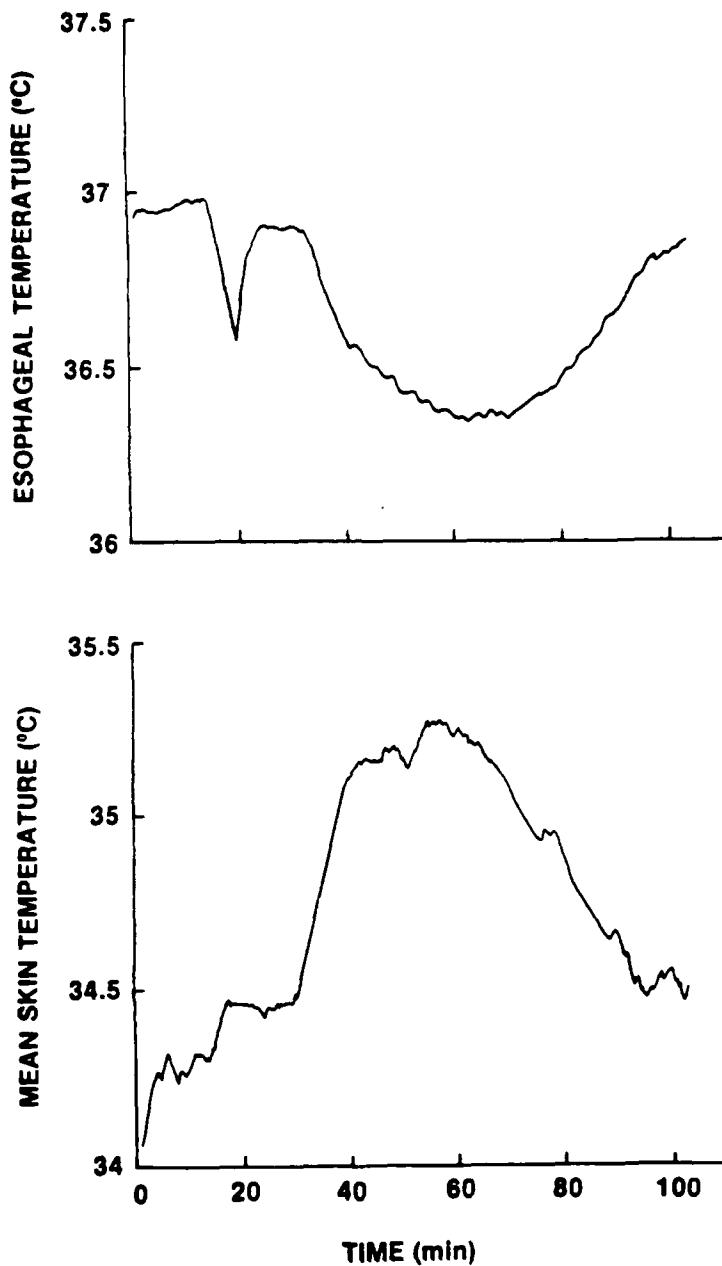


Figure 1.  $T_{es}$  and  $\bar{T}_{sk}$  as function of time for Subject 1.

Mean body temperature ( $\bar{T}_b$ ) decreased  $0.2^\circ\text{C}$  at peak FBF and decreased another  $0.1^\circ\text{C}$  by the time  $T_{es}$  was minimal ( $p \leq 0.0005$ ). Metabolic heat production was not significantly different with niacin treatment (Table 1). Fig 1 shows  $T_{es}$  and  $\bar{T}_{sk}$  as a function of time for one subject.

At peak FBF with niacin treatment, heart rate increased 8  $\text{beats} \cdot \text{min}^{-1}$  ( $p \leq 0.0005$ ) and maximally increased 13  $\text{beats} \cdot \text{min}^{-1}$  (Table

2). Mean arterial pressure (MAP) decreased about 1 kPa at peak FBF with niacin treatment ( $p \leq 0.0005$ ). Eventually, MAP decreased by an average of 1.65 kPa with niacin treatment (Table 2). Fig. 2 shows FBF, MAP and heart rate as a function of time for one subject.

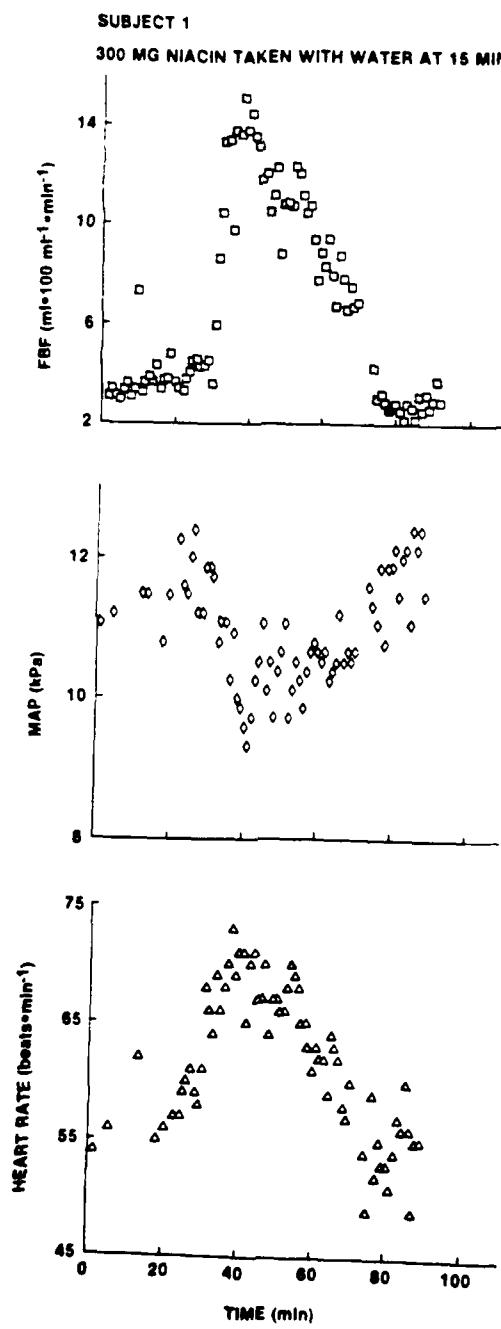


Figure 2. FBF, MAP and heart rate as a function of time for Subject 1.

**Table 2.** Mean ( $\pm$ SD) cardiovascular control data, niacin data at peak FBF, and niacin data at peak response.

	Control	Niacin (peak FBF)	Niacin (peak response)
HR (beats $\cdot$ min $^{-1}$ )	53(7)	61(6) <sup>a</sup>	67(5) <sup>a</sup>
MAP (kPa)	11.36(0.3)	10.29(0.2) <sup>b</sup>	9.71(0.3) <sup>b</sup>

<sup>a</sup>Niacin treatment different from control ( $p \leq 0.0005$ )

<sup>b</sup>All different ( $p \leq 0.0005$ )

#### DISCUSSION

In this investigation the effects of niacin were studied in resting, seated volunteers in order to eliminate the influence of upright posture on blood pressure. The dose of niacin used in this study ( $5 \text{ mg} \cdot \text{kg}^{-1}$  body weight) was sufficient to achieve prolonged cutaneous vasodilation and it also caused  $T_{\text{ss}}$  to decrease

for an average time of 53 min. By this design, the cardiovascular and thermoregulatory effects of niacin could be studied without subjecting the volunteers to a clinical dose of niacin.

Although the cutaneous vasodilatory action of niacin has been known for years<sup>10</sup>, the increased sensible heat flux due to cutaneous vasodilation had not been quantified previously. In the present study, skin blood flow was measured in the forearm of resting, semi-upright humans and shown to be significantly increased after niacin treatment. At first glance, the data from the current study appear to support the hypothesis that niacin is an effective thermoregulatory aid because  $R+C$  increased and  $T_{\text{ss}}$  rapidly decreased. Yet, the substantial reduction in MAP and increased heart rate observed with niacin treatment indicated that the thermoregulatory data cannot be considered independently. In the seated posture, MAP was adequate, but these data indicated that the effect of niacin on blood pressure was not trivial. Had the subjects been in an upright posture, MAP may have been reduced to the point that syncope might have occurred. It is reasonable to assume that the increased heart rate observed was a compensatory response to maintain cardiac output as the proportion of total blood volume in the skin increased.

There is a potential risk that hypothermia could develop in normal subjects if niacin were ingested in an environment in which ambient temperature was much less than  $T_{\text{ss}}$ . In the present study,  $T_{\text{ss}}$  was approximately  $4^{\circ}\text{C}$  less than  $T_{\text{ss}}$ , yet  $T_{\text{ss}}$  decreased  $0.55^{\circ}\text{C}$ . As the temperature gradient between the skin and environment increases,  $T_{\text{ss}}$  would decrease proportionally.

Clinical doses (1-7 g) of niacin are used in the treatment of hyperlipoproteinemia and hypertriglyceridemia<sup>11</sup>, and it has been suggested<sup>12</sup> that the use of niacin as a pretreatment before cooling therapy in emergency treatment of heat stroke may be feasible. In many clinical uses of niacin, the vasodilatory action of niacin is blocked by pretreatment with aspirin<sup>13</sup>. If aspirin is not used as a pretreatment, caution is advised with niacin treatment because of its potent vasodilatory effect. The present study clearly shows significantly decreased MAP which would contraindicate its

use' as a pretreatment to cooling therapy in heat stroke. Recently, it was reported that clinical doses of niacin increased the risk of atrial fibrillation and arrhythmias", so use of smaller amounts of niacin as a thermoregulatory aid during rest or exercise must be carefully explored. It is imperative that the interpretation of the results of the current study be limited to the specific population studied, the posture and resting status of that population and the specific environmental conditions of the study.

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The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation. Human subjects participated in these studies after giving their informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

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